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=> s (sandberg b?/au or nilsson r?/au)
L1 1901 (SANDBERG B?/AU OR NILSSON R?/AU)

=> s l1 and trifunctional crosslinking
L2 4 L1 AND TRIFUNCTIONAL CROSSLINKING

=> s l2 and biotin
L3 4 L2 AND BIOTIN

=> s l3 and anti-Erb
L4 1 L3 AND ANTI-ERB

=> d l4 cbib abs

L4 ANSWER 1 OF 1 HCAPLUS COPYRIGHT 2010 ACS on STN
2005:493522 Document No. 143:32224 Immunoconjugates for targeting of ERB antigens. **Sandberg, Bengt E. B.; Nilsson, Rune** (Mitra Medical AB, Swed.). PCT Int. Appl. WO 2005051424 A1 20050609, 67 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IS, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2004-SE1753 20041126. PRIORITY: US 2003-525703P 20031128; SE 2003-3229 20031128.

AB A conjugate comprising a) a **trifunctional crosslinking** moiety, to which is coupled b) an affinity ligand via a linker 1, c) a cytotoxic agent, optionally via a linker 2, and d) an **anti Erb** antibody or variants thereof having the ability to bind to Erb antigens expressed on mammalian tumor surfaces with an affinity-binding constant of at least 5x106M-1, wherein the affinity ligand is **biotin** , or a **biotin** derivative having essentially the same binding

function to avidin or streptavidin as **biotin**, wherein stability towards enzymic cleavage of the biotinamide bond has been introduced in linker 1.

=> dup remove l3
PROCESSING COMPLETED FOR L3
L5 4 DUP REMOVE L3 (0 DUPLICATES REMOVED)

=> d l5 1-4 cbib abs

L5 ANSWER 1 OF 4 HCAPLUS COPYRIGHT 2010 ACS on STN
2005:493522 Document No. 143:32224 Immunoconjugates for targeting of ERB antigens. **Sandberg, Bengt E. B.; Nilsson, Rune** (Mitra Medical AB, Swed.). PCT Int. Appl. WO 2005051424 A1 20050609, 67 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IS, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2004-SE1753 20041126. PRIORITY: US 2003-525703P 20031128; SE 2003-3229 20031128.

AB A conjugate comprising a) a **trifunctional crosslinking** moiety, to which is coupled b) an affinity ligand via a linker 1, c) a cytotoxic agent, optionally via a linker 2, and d) an anti Erb antibody or variants thereof having the ability to bind to Erb antigens expressed on mammalian tumor surfaces with an affinity-binding constant of at least 5x106M-1, wherein the affinity ligand is **biotin**, or a **biotin** derivative having essentially the same binding function to avidin or streptavidin as **biotin**, wherein stability towards enzymic cleavage of the biotinamide bond has been introduced in linker 1.

L5 ANSWER 2 OF 4 HCAPLUS COPYRIGHT 2010 ACS on STN
2001:923565 Document No. 136:42919 **Biotin** derivatives for an extracorporeal device. **Sandberg, Bengt**; Wilbur, Scott; **Nilsson, Rune** (Mitra Medical Technology AB, Swed.; University of Washington). PCT Int. Appl. WO 2001095857 A2 20011220, 45 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, CZ, DE, DE, DK, DK, DM, DZ, EC, EE, EE, ES, FI, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-SE1374 20010618. PRIORITY: SE 2000-2287 20000616; US 2000-216625P 20000707.

AB A method for the conditioning of an extracorporeal device is described, as well as a method for extracorporeal extraction of toxic material from mammalian body fluids in connection with diagnosis or treatment of a mammalian condition or disease. The methods comprise (i) a solution containing a reagent comprising **biotin** moieties, such as natural **biotin** or its derivs., and a toxin-binding moiety, (ii) linkers and a **trifunctional crosslinking** moiety, and (ii) an extracorporeal device comprising said reagent. For example, a dibiotin compound, 1-isothiocyanato-3,5-bis-(13'-biotinamidyl-4',7',10'-trioxatridecanamidyl)-aminoisophthalate was prepared and conjugated with a toxin-binding mol., i.e., monoclonal antibody 53-6A2. A dibiotin-toxin-binding conjugate was used for conditioning of an

avidin-agarose column suitable for removal of toxins from blood.

L5 ANSWER 3 OF 4 HCAPLUS COPYRIGHT 2010 ACS on STN
2000:35037 Document No. 132:90367 Trifunctional reagent for conjugation to a biomolecule for use in diagnosis and therapy. Wilbur, D. Scott; **Sandberg, Bengt E. B.** (University of Washington, USA; Mitra Medical Technology AB). PCT Int. Appl. WO 2000002051 A1 20000113, 48 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, CZ, DE, DE, DK, DK, EE, EE, ES, FI, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1999-SE1241 19990707. PRIORITY: SE 1998-1345 19980707.

AB A reagent for conjugation to a biomol. for diagnosis and treatment of human and animal conditions and diseases is described, wherein the reagent is a single mol. with at least three functional parts and a) wherein a **trifunctional crosslinking** moiety is coupled to b) an affinity ligand via a linker 1, said affinity ligand being capable of binding with another mol. having affinity for said ligand; to c) an effector agent, optionally via a linker 2, said effector agent exerting its effects on cells, tissues and/or humorous mols. in vivo or ex vivo; and to d) a biomol. reactive moiety, optionally via a linker 3, said moiety being capable of forming a bond between the reagent and the biomol. The affinity ligand is especially **biotin** or a **biotin** derivative The effector agent is a toxin, an enzyme capable of converting a prodrug to an active drug, an immunosuppressant, an immunostimulant, or a radionuclide-binding agent, with or without the radionuclide.

L5 ANSWER 4 OF 4 HCAPLUS COPYRIGHT 2010 ACS on STN
2000:35036 Document No. 132:90366 Trifunctional reagent for conjugation to a biomolecule for use in diagnosis and therapy. Wilbur, D. Scott; **Sandberg, Bengt E. B.** (University of Washington, USA; Mitra Medical Technology AB). PCT Int. Appl. WO 2000002050 A1 20000113, 41 pp. DESIGNATED STATES: W: AL, AM, AT, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, CZ, DE, DE, DK, DK, EE, EE, ES, FI, FI, GB, GE, GH, GM, GW, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1998-SE1345 19980707.

AB A reagent for conjugation to a biomol. for diagnosis and treatment of human and animal conditions and diseases is described, wherein the reagent is a single mol. with at least three functional parts and a) wherein a **trifunctional crosslinking** moiety is coupled to b) an affinity ligand via a linker 1, said affinity ligand being capable of binding with another mol. having affinity for said ligand; to c) an effector agent, optionally via a linker 2, said effector agent exerting its effects on cells, tissues and/or humorous mols. in vivo or ex vivo; and to d) a biomol. reactive moiety, optionally via a linker 3, said moiety being capable of forming a bond between the reagent and the biomol. The affinity ligand is especially **biotin** or a **biotin** derivative The effector agent is a toxin, an enzyme capable of converting a prodrug to an active drug, an immunosuppressant, an immunostimulant, or a radionuclide-binding agent, with or without the radionuclide.

=> s trifunctional crosslinker
L6 60 TRIFUNCTIONAL CROSSLINKER

```
=> s l6 and biotin
L7            6 L6 AND BIOTIN

=> s l7 and anti-erbB
L8            0 L7 AND ANTI-ERBB

=> dup remove l7
PROCESSING COMPLETED FOR L7
L9            2 DUP REMOVE L7 (4 DUPLICATES REMOVED)

=> d l9 1-2 cbib abs

L9   ANSWER 1 OF 2  HCAPLUS  COPYRIGHT 2010 ACS on STN
2006:367724   Document No. 145:6459  Identification of the annexin A2
     heterotetramer as a receptor for the plasmin-induced signaling in human
     peripheral monocytes.  Laumonnier, Yves; Syrovets, Tatiana; Burysek,
     Ladislav; Simmet, Thomas (Department of Pharmacology of Natural Products
     and Clinical Pharmacology, University of Ulm, Germany).  Blood, 107(8),
     3342-3349 (English) 2006.  CODEN: BLOOAW.  ISSN: 0006-4971.  Publisher:
     American Society of Hematology.
AB   We have previously demonstrated that plasmin acts as a potent
     proinflammatory activator of human peripheral monocytes.  Here we identify
     the annexin A2 heterotetramer, composed of annexin A2 and S100A10, as a
     receptor for the plasmin-induced signaling in human monocytes.  Monocytes
     express the annexin A2 heterotetramer on the cell surface as shown by flow
     cytometry, fluorescence microscopy, and coimmunopptn. of biotinylated cell
     surface proteins.  Binding of plasmin to annexin A2 and S100A10 on
     monocytes was verified by biotin transfer from plasmin labeled
     with a trifunctional crosslinker.  Antibodies directed
     against annexin A2 or S100A10 inhibited the chemotaxis elicited by
     plasmin, but not that induced by fMLP.  Further, down-regulation of
     annexin A2 or S100A10 in monocytes by antisense oligodeoxynucleotides
     impaired the chemotactic response to plasmin, but not that to fMLP.
     Antisense oligodeoxynucleotides similarly decreased the TNF-α
     release by plasmin-stimulated, but not by LPS-stimulated, monocytes.  At
     the mol. level, stimulation with plasmin, but not with catalytically
     inactivated plasmin, induced cleavage of annexin A2 and dissociation of the
     heterotetramer complex.  Substitution of lysine to alanine in position 27
     abolished the cleavage of recombinant annexin A2 in vitro.  Together,
     these data identify the annexin A2 heterotetramer as a signaling receptor
     activated by plasmin via proteolysis.

L9   ANSWER 2 OF 2     MEDLINE on STN                    DUPLICATE 1
2006358933.    PubMed ID: 16772401.  Identifying an interaction site between
     MutH and the C-terminal domain of MutL by crosslinking, affinity
     purification, chemical coding and mass spectrometry. Ahrends Robert;
     Kosinski Jan; Kirsch Dieter; Manelyte Laura; Giron-Monzon Luis; Hummerich
     Lars; Schulz Oliver; Spengler Bernhard; Friedhoff Peter. (Institut fur
     Biochemie (FB 08), Justus-Liebig-Universitat, D-35392 Giessen, Germany. )
     Nucleic acids research, (2006) Vol. 34, No. 10, pp. 3169-80.  Electronic
     Publication: 2006-06-13. Journal code: 0411011. E-ISSN: 1362-4962. L-ISSN:
     0305-1048.
     Report No.: NLM-PMC1483222. Pub. country: England: United Kingdom.
     Language: English.
AB   To investigate protein-protein interaction sites in the DNA mismatch
     repair system we developed a crosslinking/mass spectrometry technique
     employing a commercially available trifunctional
     crosslinker with a thiol-specific methanethiosulfonate group, a
     photoactivatable benzophenone moiety and a biotin affinity tag.
     The XACM approach combines photocrosslinking (X), in-solution digestion of
     the crosslinked mixtures, affinity purification via the biotin
```

handle (A), chemical coding of the crosslinked products (C) followed by MALDI-TOF mass spectrometry (M). We illustrate the feasibility of the method using a single-cysteine variant of the homodimeric DNA mismatch repair protein MutL. Moreover, we successfully applied this method to identify the photocrosslink formed between the single-cysteine MutH variant A223C, labeled with the **trifunctional crosslinker** in the C-terminal helix and its activator protein MutL. The identified crosslinked MutL-peptide maps to a conserved surface patch of the MutL C-terminal dimerization domain. These observations are substantiated by additional mutational and chemical crosslinking studies. Our results shed light on the potential structures of the MutL holoenzyme and the MutH-MutL-DNA complex.

=> s l6 and affinity ligand
L10 0 L6 AND AFFINITY LIGAND

=> s l6 and antibod?
L11 6 L6 AND ANTIBOD?

=> dup remove l11
PROCESSING COMPLETED FOR L11
L12 4 DUP REMOVE L11 (2 DUPLICATES REMOVED)

=> d l12 1-4 cbib abs

L12 ANSWER 1 OF 4 MEDLINE on STN DUPLICATE 1
2009531071. PubMed ID: 19579256. Improvement of targeted gene delivery to human cancer cells by a novel **trifunctional crosslinker**. Shiota Maki; Shamsur Lahman; Kawahara Shun-ichi; Wadhwa Renu; Ikeda Yutaka. (National Institute of Advanced Industrial Science and Technology (AIST), Central 4, 1-1-1 Higashi, Tsukuba, Ibaraki 305-8562, Japan.) Chemistry, an Asian journal, (2009 Aug 3) Vol. 4, No. 8, pp. 1318-22. Journal code: 101294643. E-ISSN: 1861-471X. Pub. country: Germany: Germany, Federal Republic of. Language: English.

AB A facile method for the construction of an immunoconjugate which displays targeting ligands, such as **antibody** fragments, with a high density is reported. For this purpose, we synthesized a novel trifunctional crosslinking reagent. By the use of this reagent, ligands targeting the specific cell can be displayed on the surface of the drug carrier with a high density. In this study, we display HER2 (human epidermal growth-factor receptor-2) binding ligands on branched polyethylenimine (PEI), which can form polyplexes with plasmid DNA. Kinetic analysis of the binding to the extracellular domain of HER2 show the PEI displaying a high density of ligands binds to the target more strongly compared to the PEI displaying ligands at a low density. The increased density of HER2 ligands displayed on the gene carrier contributes to the improved transfection efficiency. This approach can be applied to other drug delivery systems, including liposome, micelle, and so on.

L12 ANSWER 2 OF 4 HCAPLUS COPYRIGHT 2010 ACS on STN
2006:367724 Document No. 145:6459 Identification of the annexin A2 heterotetramer as a receptor for the plasmin-induced signaling in human peripheral monocytes. Laumonnier, Yves; Syrovets, Tatiana; Burysek, Ladislav; Simmet, Thomas (Department of Pharmacology of Natural Products and Clinical Pharmacology, University of Ulm, Germany). Blood, 107(8), 3342-3349 (English) 2006. CODEN: BLOOAW. ISSN: 0006-4971. Publisher: American Society of Hematology.

AB We have previously demonstrated that plasmin acts as a potent proinflammatory activator of human peripheral monocytes. Here we identify the annexin A2 heterotetramer, composed of annexin A2 and S100A10, as a

receptor for the plasmin-induced signaling in human monocytes. Monocytes express the annexin A2 heterotetramer on the cell surface as shown by flow cytometry, fluorescence microscopy, and coimmunopptn. of biotinylated cell surface proteins. Binding of plasmin to annexin A2 and S100A10 on monocytes was verified by biotin transfer from plasmin labeled with a **trifunctional crosslinker**. **Antibodies** directed against annexin A2 or S100A10 inhibited the chemotaxis elicited by plasmin, but not that induced by fMLP. Further, down-regulation of annexin A2 or S100A10 in monocytes by antisense oligodeoxynucleotides impaired the chemotactic response to plasmin, but not that to fMLP. Antisense oligodeoxynucleotides similarly decreased the TNF-α release by plasmin-stimulated, but not by LPS-stimulated, monocytes. At the mol. level, stimulation with plasmin, but not with catalytically inactivated plasmin, induced cleavage of annexin A2 and dissociation of the heterotetramer complex. Substitution of lysine to alanine in position 27 abolished the cleavage of recombinant annexin A2 in vitro. Together, these data identify the annexin A2 heterotetramer as a signaling receptor activated by plasmin via proteolysis.

L12 ANSWER 3 OF 4 HCAPLUS COPYRIGHT 2010 ACS on STN
2005:192731 Chemical crosslinkers for the study of multivalent protein-ligand interactions. Yang, Jerry; Bautista, Mahealani R.; Inbar, Petra (Department of Chemistry and Biochemistry, University of California, San Diego, La Jolla, CA, 92093-0358, USA). Abstracts of Papers, 229th ACS National Meeting, San Diego, CA, United States, March 13-17, 2005, ORGN-711. American Chemical Society: Washington, D. C. (English) 2005. CODEN: 69GQMP.

AB Multivalent interactions are ubiquitous in biol. systems. The multivalent binding of **antibodies** to antigens on the surface of cells, for instance, is a common characteristic of immune recognition. It has been shown that synthetic divalent antigens form multimeric aggregates with **antibodies**, presumably through the multivalent binding of **antibodies** to antigens. This work presents the synthesis and use of a water soluble **trifunctional crosslinker** to prepare divalent antigens capable of carrying a variety of chemical groups. These trifunctionalized crosslinkers will be used to probe the details of the observed multivalent **antibody**-antigen complexes. The objective of this research is to use synthetic multivalent mols. to elucidate the mechanistic details of small mol.-induced aggregation of proteins, and to incorporate multivalency in the design of new therapeutic drugs.

L12 ANSWER 4 OF 4 BIOSIS COPYRIGHT (c) 2010 The Thomson Corporation on STN
2006:281192 Document No.: PREV200600279865. Chemical crosslinkers for the study of multivalent protein-ligand interactions. Yang, Jerry [Reprint Author]; Bautista, Mahealani R.; Inbar, Petra. Univ Calif San Diego, Dept Chem and Biochem, La Jolla, CA 92093 USA. jerryyang@ucsd.edu; mrbautis@ucsd.edu. Abstracts of Papers American Chemical Society, (MAR 13 2005) Vol. 229, No. Part 2, pp. U540-U541.
Meeting Info.: 229th National Meeting of the American-Chemical-Society. San Diego, CA, USA. March 13 -17, 2005. Amer Chem Soc.
CODEN: ACSRAL. ISSN: 0065-7727. Language: English.

=> s triaminobenzene
L13 516 TRIAMINOBENZENE

=> s l13 and biotin
L14 3 L13 AND BIOTIN

=> s l14 and targeting
L15 2 L14 AND TARGETING

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=> dup remove l15
PROCESSING COMPLETED FOR L15
L16            2 DUP REMOVE L15 (0 DUPLICATES REMOVED)

=> d l16 1-2 cbib abs

L16  ANSWER 1 OF 2  HCAPLUS  COPYRIGHT 2010 ACS on STN
2000:35037  Document No. 132:90367  Trifunctional reagent for conjugation to a
     biomolecule for use in diagnosis and therapy.  Wilbur, D. Scott; Sandberg,
     Bengt E. B. (University of Washington, USA; Mitra Medical Technology AB).
     PCT Int. Appl. WO 2000002051 A1 20000113, 48 pp.  DESIGNATED STATES: W:
     AE, AL, AM, AT, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, CZ,
     DE, DE, DK, DK, EE, EE, ES, FI, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL,
     IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK,
     MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK, SL, TJ, TM,
     TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ,
     TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA,
     GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG.  (English).
     CODEN: PIXXD2.  APPLICATION: WO 1999-SE1241 19990707.  PRIORITY: SE
     1998-1345 19980707.
AB   A reagent for conjugation to a biomol. for diagnosis and treatment of
     human and animal conditions and diseases is described, wherein the reagent
     is a single mol. with at least three functional parts and a) wherein a
     trifunctional crosslinking moiety is coupled to b) an affinity ligand via
     a linker 1, said affinity ligand being capable of binding with another
     mol. having affinity for said ligand; to c) an effector agent, optionally
     via a linker 2, said effector agent exerting its effects on cells, tissues
     and/or humorous mols. in vivo or ex vivo; and to d) a biomol. reactive
     moiety, optionally via a linker 3, said moiety being capable of forming a
     bond between the reagent and the biomol.  The affinity ligand is especially
     biotin or a biotin derivative  The effector agent is a
     toxin, an enzyme capable of converting a prodrug to an active drug, an
     immunosuppressant, an immunostimulant, or a radionuclide-binding agent,
     with or without the radionuclide.

L16  ANSWER 2 OF 2  HCAPLUS  COPYRIGHT 2010 ACS on STN
2000:35036  Document No. 132:90366  Trifunctional reagent for conjugation to a
     biomolecule for use in diagnosis and therapy.  Wilbur, D. Scott; Sandberg,
     Bengt E. B. (University of Washington, USA; Mitra Medical Technology AB).
     PCT Int. Appl. WO 2000002050 A1 20000113, 41 pp.  DESIGNATED STATES: W:
     AL, AM, AT, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, CZ, DE,
     DE, DK, DK, EE, EE, ES, FI, FI, GB, GE, GH, GM, GW, HR, HU, ID, IL, IS,
     JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW,
     MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK, SL, TJ, TM, TR, TT,
     UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT,
     BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE,
     IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG.  (English).  CODEN:
     PIXXD2.  APPLICATION: WO 1998-SE1345 19980707.
AB   A reagent for conjugation to a biomol. for diagnosis and treatment of
     human and animal conditions and diseases is described, wherein the reagent
     is a single mol. with at least three functional parts and a) wherein a
     trifunctional crosslinking moiety is coupled to b) an affinity ligand via
     a linker 1, said affinity ligand being capable of binding with another
     mol. having affinity for said ligand; to c) an effector agent, optionally
     via a linker 2, said effector agent exerting its effects on cells, tissues
     and/or humorous mols. in vivo or ex vivo; and to d) a biomol. reactive
     moiety, optionally via a linker 3, said moiety being capable of forming a
     bond between the reagent and the biomol.  The affinity ligand is especially
     biotin or a biotin derivative  The effector agent is a
     toxin, an enzyme capable of converting a prodrug to an active drug, an
     immunosuppressant, an immunostimulant, or a radionuclide-binding agent,
     with or without the radionuclide.
```

```
=> s tricarboxylbenzene
L17          0 TRICARBOXYLBENZENE

=> s tricarboxylbenzene
L18          0 TRICARBOXYLBENZENE

=> s dicarboxyanyline
L19          0 DICARBOXYANYLINE

=> s diamino benzoic acid
L20         88 DIAMINO BENZOIC ACID

=> s l20 and biotin
L21          2 L20 AND BIOTIN

=> dup remove l21
PROCESSING COMPLETED FOR L21
L22           2 DUP REMOVE L21 (0 DUPLICATES REMOVED)

=> d l22 1-2 cbib abs

L22  ANSWER 1 OF 2  HCAPLUS  COPYRIGHT 2010 ACS on STN
2003:334855   Document No. 138:343814  Multidrug multiligand conjugates for
     targeted drug delivery.  Safavy, Ahmad (The UAB Research Foundation, USA).
       PCT Int. Appl. WO 2003035011 A2 20030501, 25 pp.  DESIGNATED STATES: RW:
     AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE,
     TR.  (English).  CODEN: PIXXD2.  APPLICATION: WO 2002-US34548 20021028.
     PRIORITY: US 2001-348299P 20011026.
AB   Described is a multi drug multiligand conjugate for targeted drug
     delivery.  The MDML conjugate contains a plurality of tripartite mols.
     linked to a central scaffold moiety, with each tripartite mol. comprising
     a targeting mol., a therapeutic agent and a scaffold-binding element.  The
     MDML conjugate allows for more efficient delivery of therapeutic agents to
     the cells resulting in enhanced therapeutic efficiency.  A model MDML
     conjugate is disclosed as well as method for the synthesis of the model
     conjugate.

L22  ANSWER 2 OF 2  HCAPLUS  COPYRIGHT 2010 ACS on STN
1999:147950   Document No. 130:206994  Pyrazine derivatives formed by the
     reaction of deoxyglucosone with diamino derivatives, antibodies
     recognizing the product and application in diabetes diagnosis.  Uchida,
     Yoshiaki; Kurano, Yoshihiro; Ito, Satoru (Fujirebio, Inc., Japan).  Ger.
     Offen. DE 19837664 A1 19990225, 22 pp.  (German).  CODEN: GWXXBX.
     APPLICATION: DE 1998-19837664 19980819.  PRIORITY: JP 1997-240348
     19970821.
GI
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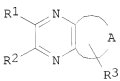
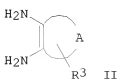


I



II

AB The invention concerns a monoclonal antibody that recognizes pyrazine derivs. (I) that are formed when a diamino derivative (II) is reacting with a 1,2-dicarbonyl derivative, e.g. deoxyglucosone, an in vivo intermediate involved in the nonenzymic glycation of proteins causing diabetic

complications. Monoclonal antibodies are raised using I type immunogens and are immobilized after purification II compds. are labeled at R3, thus when binding to the antibody they can be detected. In I and II the groups are the following: R1 and R2 = H, Me, trihydroxypropyl, dihydroxypropyl, hydroxymethyl; R3 = a spacer group plus a reactive label to form covalent bonds, e.g. carboxyl, hydroxy, sulfhydryl, amino, maleinimide, aldehyde, halogen, **biotin**, etc.; A = pyridine, benzene, furan. Typical 1,2-dicarbonyl compds. that react with II are deoxyglucosone and methylglyoxal. The invention also concerns a test kit that contains the antibody, the carrier to immobilize the antibody and a labeled diamino compound II. Diamino derivs. were synthesized, reacted with deoxyglucosone and coupled to keyhole limpet hemocyanin to immunize mice; monoclonal antibodies were isolated and used in immunoassays. Synthesized diamino derivs. were also labeled with **biotin** and used as reagents to determine deoxyglucosone using the antibodies immobilized on ELISA plates.

```
=> s "mitraTag"
L23           3 "MITRATAG"

=> dup remove l23
PROCESSING COMPLETED FOR L23
L24           3 DUP REMOVE L23 (0 DUPLICATES REMOVED)

=> d l24 1-3 cbib as
'AS' IS NOT A VALID FORMAT FOR FILE 'EMBASE'

The following are valid formats:

The default display format is BIB.

ABS --------- AB
ALL --------- AN, CP, TI, AU, CS, SO, PB, PUI, CY, DT, FS, NCT, LA, SL,
              ED, AB, CT, ST, RN, CN, NP, CO, GEN
BIB --------- AN, CP, TI, AU, CS, SO, PB, PUI, CY, DT, FS, NCT, LA, SL,
              ED
CBIB -------- Compressed bibliographic data
DALL -------- ALL, delimited for post-processing
IABS -------- ABS, with a text label
IALL -------- ALL, indented with text labels
IBIB -------- BIB, indented with text labels
IND --------- CT, ST, RN, CN, NP, CO, GEN
TRIAL ------  TI, CT, ST, RN, CN, NP, CO, GEN
  (SAM, TRI, FREE, SCAN)
HIT --------- All fields containing hit terms
HITIND ------ IND
KWIC -------- All hit terms plus 20 words on either side
OCC --------- List of display fields containing hit terms
              and number of occurrences in each field

Hit terms will be highlighted in all displayable fields.

To display a particular field or fields, enter the display field
codes. For a list of display field codes, enter 'HELP DFIELDS'
at an arrow prompt (=>). Examples of formats include: 'BIB';
'AB'; 'SO,AB'. You may specify the format fields in any order,
and the information will be displayed in the same order as the
format specification.

The same formats (except for HIT, HITIND, KWIC, and OCC) may be
used with the DISPLAY ACC command to display the record for a
specified Accession Number.
```

ENTER DISPLAY FORMAT (BIB):abs

L24 ANSWER 1 OF 3 EMBASE COPYRIGHT (c) 2010 Elsevier B.V. All rights reserved on STN

AB The aim of this study was to evaluate the possibility of decreasing the myelotoxicity associated with radioimmunotherapy (RIT) by extracorporeal depletion of radioimmunoconjugates (RIC) from the circulation. The optimal combination of radionuclide and the time interval between injection of the RIC and the subsequent extracorporeal depletion procedure was assessed in immunocompetent rats, with respect to both myelotoxicity and tumor concentration of RIC. Methods: Rats were injected with 177Lu- or 90Y-labeled antibody conjugate (mAb-DOTA-biotin) (mAb is monoclonal antibody; DOTA is 1,4,7,10-tetraazacyclododecane-N,N',N",N"'- tetraacetic acid) and subjected to removal of the conjugate from the circulation by extracorporeal affinity adsorption treatment (ECAT) 12, 24, or 48 h after injection. Myelotoxicity was assessed by analysis of blood parameters for 10 wk. The effect of ECAT on the tumor concentration of RIC was evaluated in parallel by scintillation camera imaging in rats injected with 111In-labeled RIC. Results: ECAT reduced the blood content of RIC by 95%. Thus, myelotoxicity was significantly milder in animals subjected to ECAT than that in controls. The timing of ECAT influenced the rate and level of bone marrow recovery, with an earlier recovery in animals subjected to ECAT early after injection. The toxicity-reducing effect of ECAT was more distinct in animals injected with 177Lu-labeled RIC than in animals injected with 90Y- labeled RIC. Scintillation camera imaging of tumors before and after ECAT revealed that subjecting animals to ECAT at 12 h after injection considerably reduced the total activity in tumors (34%), whereas the effect was lower at both 24 h (18%) and 48 h (18%) after injection. Conclusion: ECAT can efficiently reduce myelotoxicity associated with RIT, and the concentration of RIC in tumor can be sustained, provided ECAT is performed at an optimal time after antibody administration. The choice of radionuclide for RIT in combination with ECAT is important, as the physical half-life is crucial for the toxicity-reducing potential of ECAT at a specific time. Copyright .COPYRGT. 2007 by the Society of Nuclear Medicine, Inc.

L24 ANSWER 2 OF 3 EMBASE COPYRIGHT (c) 2010 Elsevier B.V. All rights reserved on STN

AB Purpose: Knowledge of the blood pharmacokinetics of monoclonal antibodies is crucial in deciding the optimal time for starting the administration of a "clearing agent" or using a "clearing device." The primary purpose was to investigate whether the pharmacokinetics of various antibodies labeled with the same chelator and 111In differed significantly after i.v. injection in immunocompetent rats. A new trifunctional chelator called "1033" containing a biotin and a radiometal chelation moiety is introduced, making it possible to use only one conjugation procedure for the antibody. Experimental Design: Sixty-five non-tumor-bearing rats were included and divided into four groups (I-IV). The blood pharmacokinetics was investigated for rituximab, BR96, and trastuzumab labeled with 1033 and 111In (I-III). The whole-body activity and activity uptake in muscle, liver, and kidney, which might explain differences in the early pharmacokinetics in blood, were also measured. hMN14 labeled with another chelator [1,4,7,10- tetraazacyclododecane-N,N',N",N"'-tetraacetic acid (DOTA)], but with the same radionuclide (111In-biotin-DOTA-hMN14), was studied (IV). The blood pharmacokinetics from another 15 tumor-bearing rats was compared with those of non - tumor-bearing rats (III) by injection of 111In-1033-BR96. Results: No statistical difference was detected between the groups regarding the blood pharmacokinetics of rituximab, BR96, or trastuzumab. The pharmacokinetics and biodistribution of 111In- biotin-DOTA-hMN14 exhibited a clear difference compared with others. There were no significant differences in the blood

pharmacokinetics of 111In- 1033-BR96 between tumor-bearing rats and non - tumor-bearing rats. Conclusions: Different antibodies labeled with the trifunctional chelator 1033 and 111In did not exhibit different blood pharmacokinetics, which means that the pharmacokinetics could be predicted irrespective of the IgG1 antibody chosen. A small tumor burden did not change the pharmacokinetics of the radioimmunoconjugates. .COPYRGT. 2005 American Association for Cancer Research.

L24 ANSWER 3 OF 3 EMBASE COPYRIGHT (c) 2010 Elsevier B.V. All rights reserved on STN

AB Radioimmunotherapy is limited by the absorbed dose to radiosensitive organs. Removal of circulating radiolabeled MAbs after tumor tissue has been optimally targeted and should permit the administration of higher radioactivity to patients, resulting in a higher absorbed tumor dose. A novel "extracorporeal affinity adsorption treatment" (ECAT) device (MitraDep®) was tested, with which biotinylated and radiolabeled MAbs can be removed from the circulation by passing whole blood over a filter coated with avidin. The antibodies were simultaneously radiolabeled and biotinylated using a trifunctional moiety comprising DOTA and biotin. Eight patients-all but 1 of whom with aggressive or mantle cell B-cell lymphoma-who had failed to respond to standard therapies received infusions of 250 mg/m2 cold rituximab and 150 MBq 111In-rituximab-biotin for immunoscintigraphy. A week later, the patients were treated with another 250 mg/m2 rituximab followed by 111In/-90Y-rituximab-biotin (11 or 15 90Y M Bq/kg). ECAT was performed 48 hours later. All 8 patients receiving 111In-rituximab-biotin showed tumor uptake. Seven patients received radioimmunotherapy and subsequent ECAT. The mean depletion of 90Y-rituximab-biotin in whole blood after ECAT was 96%, in the whole body 49%, in the lungs 62%, and in the liver and kidneys 40%. No effects on patients' vital signs and no adverse effects on hematological or coagulation parameters was observed during the ECAT procedure. A dose-escalation study is initiated. .COPYRGT. Mary Ann Liebert, Inc.

=> d l24 1-3 cbib abs

L24 ANSWER 1 OF 3 EMBASE COPYRIGHT (c) 2010 Elsevier B.V. All rights reserved on STN

2007496055 EMBASE Reduced myelotoxicity with sustained tumor concentration of radioimmunoconjugates in rats after extracorporeal depletion.
Martensson, Linda (correspondence); Tennvall, Jan. Department of Oncology, Lund University, Lund, Sweden. linda.martensson@med.lu.se. Nilsson, Rune. Mitra Medical AB, Lund, Sweden. Ohlsson, Tomas; Strand, Sven-Erik. Department of Medical Radiation Physics, Lund University, Lund, Sweden. Sjogren, Hans-Olov. Department of Immunology, Lund University, Lund, Sweden. Martensson, Linda (correspondence). Department of Oncology, Lund University Hospital, SE-221 85 Lund, Sweden. linda.martensson@med.lu.se. Journal of Nuclear Medicine Vol. 48, No. 2, pp. 269-276 1 Feb 2007.
Refs: 26.
ISSN: 0161-5505. CODEN: JNMEAQ.
Pub. Country: United States. Language: English. Summary Language: English.
Entered STN: 20071102. Last Updated on STN: 20071102

AB The aim of this study was to evaluate the possibility of decreasing the myelotoxicity associated with radioimmunotherapy (RIT) by extracorporeal depletion of radioimmunoconjugates (RIC) from the circulation. The optimal combination of radionuclide and the time interval between injection of the RIC and the subsequent extracorporeal depletion procedure was assessed in immunocompetent rats, with respect to both myelotoxicity and tumor concentration of RIC. Methods: Rats were injected with 177Lu- or 90Y-labeled antibody conjugate (mAb-DOTA-biotin) (mAb is monoclonal antibody; DOTA is 1,4,7,10-tetraazacyclododecane-N,N',N",N"'- tetraacetic acid) and subjected to removal of the conjugate from the circulation by

extracorporeal affinity adsorption treatment (ECAT) 12, 24, or 48 h after injection. Myelotoxicity was assessed by analysis of blood parameters for 10 wk. The effect of ECAT on the tumor concentration of RIC was evaluated in parallel by scintillation camera imaging in rats injected with 111In-labeled RIC. Results: ECAT reduced the blood content of RIC by 95%. Thus, myelotoxicity was significantly milder in animals subjected to ECAT than that in controls. The timing of ECAT influenced the rate and level of bone marrow recovery, with an earlier recovery in animals subjected to ECAT early after injection. The toxicity-reducing effect of ECAT was more distinct in animals injected with 177Lu-labeled RIC than in animals injected with 90Y- labeled RIC. Scintillation camera imaging of tumors before and after ECAT revealed that subjecting animals to ECAT at 12 h after injection considerably reduced the total activity in tumors (34%), whereas the effect was lower at both 24 h (18%) and 48 h (18%) after injection. Conclusion: ECAT can efficiently reduce myelotoxicity associated with RIT, and the concentration of RIC in tumor can be sustained, provided ECAT is performed at an optimal time after antibody administration. The choice of radionuclide for RIT in combination with ECAT is important, as the physical half-life is crucial for the toxicity-reducing potential of ECAT at a specific time.

L24 ANSWER 2 OF 3 EMBASE

2005456497 EMBASE Blood pharmacokinetics of various monoclonal antibodies labeled with a new trifunctional chelating reagent for simultaneous conjugation with 1,4,7,10-tetraazacyclododecane-N,N',N",N"'-tetraacetic acid and biotin before radiolabeling.

Wang, Zhongmin; Martensson, Linda; Bendahl, Par-Ola; Tennvall, Jan (correspondence). Department of Oncology, Lund University Hospital, SE-221 85 Lund, Sweden. Jan.Tennvall@onk.lu.se. Ohlsson, Tomas; Strand, Sven-Erik. Department of Radiation Physics, Lund University, Lund, Sweden. Sjogren, Hans-Olov. Department of Tumor Immunology, Lund University, Lund, Sweden. Nilsson, Rune; Lindgren, Lars. Mitra Medical AB, Lund, Sweden. Wang, Zhongmin. Shanxi Tumor Hospital, Shanxi Tumor Radiotherapy Center, Shanxi, China.

Clinical Cancer Research Vol. 11, No. 19 II, pp. 7171s-7177s 1 Oct 2005.
Refs: 30.
ISSN: 1078-0432. CODEN: CCREF4.
Pub. Country: United States. Language: English. Summary Language: English.
Entered STN: 20051110. Last Updated on STN: 20051110

AB Purpose: Knowledge of the blood pharmacokinetics of monoclonal antibodies is crucial in deciding the optimal time for starting the administration of a "clearing agent" or using a "clearing device." The primary purpose was to investigate whether the pharmacokinetics of various antibodies labeled with the same chelator and 111In differed significantly after i.v. injection in immunocompetent rats. A new trifunctional chelator called "1033" containing a biotin and a radiometal chelation moiety is introduced, making it possible to use only one conjugation procedure for the antibody. Experimental Design: Sixty-five non-tumor-bearing rats were included and divided into four groups (I-IV). The blood pharmacokinetics was investigated for rituximab, BR96, and trastuzumab labeled with 1033 and 111In (I-III). The whole-body activity and activity uptake in muscle, liver, and kidney, which might explain differences in the early pharmacokinetics in blood, were also measured. hMN14 labeled with another chelator [1,4,7,10- tetraazacyclododecane-N,N',N",N"'-tetraacetic acid (DOTA)], but with the same radionuclide (111In-biotin-DOTA-hMN14), was studied (IV). The blood pharmacokinetics from another 15 tumor-bearing rats was compared with those of non - tumor-bearing rats (III) by injection of 111In-1033-BR96. Results: No statistical difference was detected between the groups regarding the blood pharmacokinetics of rituximab, BR96, or trastuzumab. The pharmacokinetics and biodistribution

of 111In- biotin-DOTA-hMN14 exhibited a clear difference compared with others. There were no significant differences in the blood pharmacokinetics of 111In- 1033-BR96 between tumor-bearing rats and non - tumor-bearing rats. Conclusions: Different antibodies labeled with the trifunctional chelator 1033 and 111In did not exhibit different blood pharmacokinetics, which means that the pharmacokinetics could be predicted irrespective of the IgG1 antibody chosen. A small tumor burden did not change the pharmacokinetics of the radioimmunoconjugates. .COPYRGT. 2005 American Association for Cancer Research.

L24 ANSWER 3 OF 3 EMBASE COPYRIGHT (c) 2010 Elsevier B.V. All rights reserved on STN
2005391902 EMBASE A novel platform for radioimmunotherapy: Extracorporeal depletion of biotinylated and 90Y-labeled rituximab in patients with refractory B-cell lymphoma.
Linden, Ola; Garkavij, Michael; Cavallin-Stahl, Eva; Tennvall, Jan (correspondence). Department of Oncology, Lund University Hospital, SE-221 85 Lund, Sweden. Jan.Tennvall@onk.lu.se. Kurkus, Jan. Department of Nephrology, Lund University Hospital, Lund, Sweden. Ljungberg, Michael; Ohlsson, Tomas; Strand, Sven-Erik. Department of Medical Radiation Physics, Lund University Hospital, Lund, Sweden. Nilsson, Rune; Sandberg, Bengt. Mitra Medical AB, Lund, Sweden.
Cancer Biotherapy and Radiopharmaceuticals Vol. 20, No. 4, pp. 457-466 2005.
Refs: 26.
ISSN: 1084-9785. CODEN: CBRAFJ.
Pub. Country: United States. Language: English. Summary Language: English.
Entered STN: 20050929. Last Updated on STN: 20050929
AB Radioimmunotherapy is limited by the absorbed dose to radiosensitive organs. Removal of circulating radiolabeled MAbs after tumor tissue has been optimally targeted and should permit the administration of higher radioactivity to patients, resulting in a higher absorbed tumor dose. A novel "extracorporeal affinity adsorption treatment" (ECAT) device (MitraDep®) was tested, with which biotinylated and radiolabeled MAbs can be removed from the circulation by passing whole blood over a filter coated with avidin. The antibodies were simultaneously radiolabeled and biotinylated using a trifunctional moiety comprising DOTA and biotin. Eight patients-all but 1 of whom with aggressive or mantle cell B-cell lymphoma-who had failed to respond to standard therapies received infusions of 250 mg/m2 cold rituximab and 150 MBq 111In-rituximab-biotin for immunoscintigraphy. A week later, the patients were treated with another 250 mg/m2 rituximab followed by 111In/-90Y-rituximab-biotin (11 or 15 90Y M Bq/kg). ECAT was performed 48 hours later. All 8 patients receiving 111In-rituximab-biotin showed tumor uptake. Seven patients received radioimmunotherapy and subsequent ECAT. The mean depletion of 90Y-rituximab-biotin in whole blood after ECAT was 96%, in the whole body 49%, in the lungs 62%, and in the liver and kidneys 40%. No effects on patients' vital signs and no adverse effects on hematological or coagulation parameters was observed during the ECAT procedure. A dose-escalation study is initiated. .COPYRGT. Mary Ann Liebert, Inc.

=> s site specific chelating biotin
L25 0 SITE SPECIFIC CHELATING BIOTIN

=> s "MitraTag-1033"
L26 0 "MITRATAG-1033"

=> s DOTA-trioxadiamine
L27 0 DOTA-TRIOXADIAMINE

=> s trioxadiamine-5-isothiocyanato-amino-isophatelate

```
L28          0 TRIOXADIAMINE-5-ISOTHIOCYANATO-AMINO-ISOPHATELATE

=> s trastuzumab
L29      27000 TRASTUZUMAB

=> s l29 and biotin
L30        108 L29 AND BIOTIN

=> s l30 and trifunctional crosslinker
L31          0 L30 AND TRIFUNCTIONAL CROSSLINKER

=> s l30 and trifunctional
L32          5 L30 AND TRIFUNCTIONAL

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PROCESSING COMPLETED FOR L32
L33          3 DUP REMOVE L32 (2 DUPLICATES REMOVED)

=> d l33 1-3 cbib abs

L33  ANSWER 1 OF 3  HCAPLUS  COPYRIGHT 2010 ACS on STN
2005:493522  Document No. 143:32224  Immunoconjugates for targeting of ERB
     antigens.  Sandberg, Bengt E. B.; Nilsson, Rune (Mitra Medical AB, Swed.).
       PCT Int. Appl. WO 2005051424 A1 20050609, 67 pp.  DESIGNATED STATES: W:
     AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO,
     CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR,
     HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV,
     MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO,
     RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ,
     VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE,
     DK, ES, FI, FR, GA, GB, GR, IE, IS, IT, LU, MC, ML, MR, NE, NL, PT, SE,
     SN, TD, TG, TR.  (English).  CODEN: PIXXD2.  APPLICATION: WO 2004-SE1753
     20041126.  PRIORITY: US 2003-525703P 20031128; SE 2003-3229 20031128.
AB   A conjugate comprising a) a trifunctional crosslinking moiety,
     to which is coupled b) an affinity ligand via a linker 1, c) a cytotoxic
     agent, optionally via a linker 2, and d) an anti Erb antibody or variants
     thereof having the ability to bind to Erb antigens expressed on mammalian
     tumor surfaces with an affinity-binding constant of at least 5x106M-1,
     wherein the affinity ligand is biotin, or a biotin
     derivative having essentially the same binding function to avidin or
     streptavidin as biotin, wherein stability towards enzymic
     cleavage of the biotinamide bond has been introduced in linker 1.

L33  ANSWER 2 OF 3     MEDLINE on STN                    DUPLICATE 1
2005531414.    PubMed ID: 16203818.  Blood pharmacokinetics of various
     monoclonal antibodies labeled with a new trifunctional chelating
     reagent for simultaneous conjugation with
     1,4,7,10-tetraazacyclododecane-N,N',N'',N'''-tetraacetic acid and
     biotin before radiolabeling. Wang Zhongmin; Martensson Linda;
     Nilsson Rune; Bendahl Par-Ola; Lindgren Lars; Ohlsson Tomas; Sjogren
     Hans-Olov; Strand Sven-Erik; Tennvall Jan. (Department of Oncology, Lund
     University Hospital, Sweden. ) Clinical cancer research : an official
     journal of the American Association for Cancer Research, (2005 Oct 1) Vol.
     11, No. 19 Pt 2, pp. 7171s-7177s.  Journal code: 9502500. ISSN: 1078-0432.
     L-ISSN: 1078-0432. Pub. country: United States. Language: English.
AB   PURPOSE: Knowledge of the blood pharmacokinetics of monoclonal antibodies
     is crucial in deciding the optimal time for starting the administration of
     a "clearing agent" or using a "clearing device." The primary purpose was
     to investigate whether the pharmacokinetics of various antibodies labeled
     with the same chelator and (111)In differed significantly after i.v.
     injection in immunocompetent rats.  A new trifunctional chelator
     called "1033" containing a biotin and a radiometal chelation
```

moiety is introduced, making it possible to use only one conjugation procedure for the antibody. EXPERIMENTAL DESIGN: Sixty-five non-tumor-bearing rats were included and divided into four groups (I-IV). The blood pharmacokinetics was investigated for rituximab, BR96, and **trastuzumab** labeled with 1033 and (111)In (I-III). The whole-body activity and activity uptake in muscle, liver, and kidney, which might explain differences in the early pharmacokinetics in blood, were also measured. hMN14 labeled with another chelator [1,4,7,10-tetraazacyclododecane-N,N',N'',N'''-tetraacetic acid (DOTA)], but with the same radionuclide ((111)In-**biotin**-DOTA-hMN14), was studied (IV). The blood pharmacokinetics from another 15 tumor-bearing rats was compared with those of non-tumor-bearing rats (III) by injection of (111)In-1033-BR96. RESULTS: No statistical difference was detected between the groups regarding the blood pharmacokinetics of rituximab, BR96, or **trastuzumab**. The pharmacokinetics and biodistribution of (111)In-**biotin**-DOTA-hMN14 exhibited a clear difference compared with others. There were no significant differences in the blood pharmacokinetics of (111)In-1033-BR96 between tumor-bearing rats and non-tumor-bearing rats. CONCLUSIONS: Different antibodies labeled with the **trifunctional** chelator 1033 and (111)In did not exhibit different blood pharmacokinetics, which means that the pharmacokinetics could be predicted irrespective of the IgG1 antibody chosen. A small tumor burden did not change the pharmacokinetics of the radioimmunoconjugates.

L33 ANSWER 3 OF 3 HCAPLUS COPYRIGHT 2010 ACS on STN
2005:1061884 Document No. 144:345935 Blood Pharmacokinetics of Various Monoclonal Antibodies Labeled with a New **Trifunctional** Chelating Reagent for Simultaneous Conjugation with 1,4,7,10-Tetraazacyclododecane-N,N',N'',N'''-Tetraacetic Acid and **Biotin** before Radiolabeling. Wang, Zhongmin; Martensson, Linda; Nilsson, Rune; Bendahl, Paer-Ola; Lindgren, Lars; Ohlsson, Tomas; Sjoegren, Hans-Olov; Strand, Sven-Erik; Tennvall, Jan (Department of Oncology, Lund University Hospital, Lund, Swed.). Clinical Cancer Research, 11(19, Pt. 2), 7171s-7177s (English) 2005. CODEN: CCREF4. ISSN: 1078-0432. Publisher: American Association for Cancer Research.
AB PURPOSE: Knowledge of the blood pharmacokinetics of monoclonal antibodies is crucial in deciding the optimal time for starting the administration of a "clearing agent" or using a "clearing device." The primary purpose was to investigate whether the pharmacokinetics of various antibodies labeled with the same chelator and 111In differed significantly after i.v. injection in immunocompetent rats. A new **trifunctional** chelator called "1033" containing a **biotin** and a radiometal chelation moiety is introduced, making it possible to use only one conjugation procedure for the antibody. Exptl. Design: Sixty-five non-tumor-bearing rats were included and divided into four groups (I-IV). The blood pharmacokinetics was investigated for rituximab, BR96, and **trastuzumab** labeled with 1033 and 111In (I-III). The whole-body activity and activity uptake in muscle, liver, and kidney, which might explain differences in the early pharmacokinetics in blood, were also measured. hMN14 labeled with another chelator [1,4,7,10-tetraazacyclododecane-N,N',N'',N'''-tetraacetic acid (DOTA)], but with the same radionuclide (111In-**biotin**-DOTA-hMN14), was studied (IV). The blood pharmacokinetics from another 15 tumor-bearing rats was compared with those of non-tumor-bearing rats (III) by injection of 111In-1033-BR96. RESULTS: No statistical difference was detected between the groups regarding the blood pharmacokinetics of rituximab, BR96, or **trastuzumab**. The pharmacokinetics and biodistribution of 111In-**biotin**-DOTA-hMN14 exhibited a clear difference compared with others. There were no significant differences in the blood pharmacokinetics of 111In-1033-BR96 between tumor-bearing rats and non-tumor-bearing rats. CONCLUSIONS: Different antibodies labeled with the **trifunctional** chelator 1033 and 111In did not exhibit

different blood pharmacokinetics, which means that the pharmacokinetics could be predicted irresp. of the IgG1 antibody chosen. A small tumor burden did not change the pharmacokinetics of the radioimmunoconjugates.

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